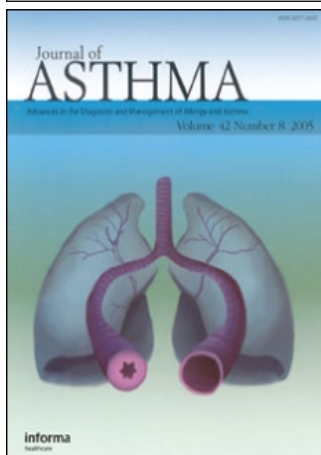


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ORIGINAL ARTICLE

Reduction of the Total IgE Level by Omalizumab in Children and Adolescents

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Background: Current data from clinical studies show that patients with severe allergic asthma experience a significant improvement from omalizumab. The early and late allergic reactions are inhibited by formation of complexes with free circulating immunoglobulin E (IgE), independent of which antigen activates the allergic cascade. The dosage of omalizumab depends on body weight and IgE level, yet no parameter has been established to guide dosage changes during therapy. The aim of this study was to investigate the value of the determination of total IgE by *ADVIA Centaur* assay to monitor the therapy progress. **Patients and Methods:** Nine patients, 8 to 17 years of age, received therapy with omalizumab due to severe allergic bronchial asthma. In addition, the patients had pronounced rhinoconjunctivitis, food allergy, insect sting allergy, and/or neurodermitis. The total IgE in the serum (*Sandwich-Immunoassay ADVIA Centaur*) was measured in the patients once monthly before each omalizumab injection as a potential progress parameter. **Results:** Six months after the beginning of therapy with omalizumab, a significant decrease of the total IgE concentration was found, in comparison to the baseline values ($p < 0.01$). In all patients, the tolerability of omalizumab was very good; there was a reduction in the frequency of the asthma exacerbations and rescue medications. The dosage of inhaled glucocorticoids could be lowered. All patients reported a clearly improved quality of life. **Conclusions:** The increase of the total IgE concentrations after administration of omalizumab described in the literature could not be confirmed. The value of total serum IgE as a progress parameter should be investigated in controlled studies with regard to sensitivity and specificity of the respective assays. The establishment of a test procedure for therapeutic monitoring appears urgently necessary, so that the appropriate dosage of omalizumab is applied in children and adolescents. Patients receiving omalizumab therapy should be closely monitored.

Keywords allergic bronchial asthma, IgE assay, omalizumab, total immunoglobulin E

INTRODUCTION

Omalizumab (*Xolair*; Novartis AG, Basel, Switzerland) has been approved in Germany since October 2005. It is a humanized monoclonal antibody that specifically blocks the binding site of immunoglobulin E (IgE) for the high-affinity IgE-receptor (FcεRI), which is able to interrupt the allergic reaction cascade at a very early timepoint and to influence potentially all IgE-mediated specific sensitizations. The binding site is located in the third domain of the heavy chain of the IgE molecules (Cε3). Omalizumab does not bind to cell-permanent IgE molecules and therefore does not work anaphylactogenically because it cannot induce degranulation of effector cells. Omalizumab lowers dosage-dependent circulating serum IgE levels by the formation of anti-IgE immune complexes (1–4).

The dosage and frequency of application (injected subcutaneously every 2 to 4 weeks) is determined by the total IgE level before the beginning of therapy and the body weight. A multilevel dosage table was developed to simplify the individual dosage and to ensure an effective reduction of the concentration of free IgE (5) (Table 1). The maximum approved dose of omalizumab is 750 mg. Although numerous case reports suggest efficacy of omalizumab even for patients with higher IgE levels, this is not covered by the current indi-

cations (6, 7). For patients with total IgE/body-weight outside the dose schema, there is currently no recommendation for omalizumab therapy.

According to the current recommendations from the asthma guidelines of the German Airway League, omalizumab is recommended as an add-on therapy for patients 12 years of age and older with severe, persisting allergic asthma (level IV) that cannot be controlled despite therapy with high-dose inhaled glucocorticoids and long-acting inhaled β_2 -sympathomimetic drugs (8). This indication probably only applies to a small proportion of pediatric patients. Therefore, it is important to report on the initial experiences with omalizumab so that further possible indications can be assessed. In particular, the value of the determination of total IgE in the serum by *ADVIA Centaur* assay (Bayer, Leverkusen, Germany) should be investigated as a potential parameter of the therapy progress.

PATIENTS AND METHODS

Study Subjects

Nine patients (6 female), 8 to 17 years of age (mean 12.1 ± 2.9 years) received omalizumab therapy for a severe, persisting, allergic bronchial asthma with sustained daily symptoms. They also showed a pronounced rhinoconjunctivitis ($n = 6$), peanut allergy ($n = 2$), insect sting allergy ($n = 1$), and/or neurodermitis ($n = 3$). Because of increased total IgE values ($n = 8$) beyond the dosage recommendations (> 750 IE/mL) or because of the young age (< 12) ($n = 4$), all 9 patients were treated after appropriate informed consent of the parents and

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TABLE 1.—Dosage overview for omalizumab in adolescent and adult asthma patients.

Baseline IgE (IU/ml)	Total milligrams of Xolair required per 2–4 week interval, Body Weight (kg)									
	>20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
>30–100	75	75	75	150	150	150	150	150	300	300
>100–200	150	150	150	300	300	300	300	300	450	600
>200–300	150	150	225	300	300	450	450	450	600	750
>300–400	225	225	300	450	450	450	600	600		
>400–500	225	300	450	450	600	600	750	750		
>500–600	300	300	450	600	600	750				
>600–700	300	450	450	600	750					

patients. In 2 patients, the dosage could be chosen according to the multi-level dosage table. In the test subjects with a serum total IgE value >750 IE/mL, the dosage was set about 30% to 50% lower than what was calculated for these cases according to the following formula: $0.016 \times \text{kgKG} \times \text{IgE}$ base value IE/ml (Table 2). Subsequently, the total IgE in the serum was measured in the patients every 6 to 8 weeks as a potential progress parameter of the omalizumab injections.

Statistical Analysis

Descriptive statistics were used to present the total IgE levels. Wilcoxon's signed rank test was performed to compare total IgE levels before versus after therapy. Statistical significance was accepted at the 5% level. Statistical analysis was performed with SPSS software (SPSS Inc, Chicago, IL, USA).

Test Principle

The instrumentation and other reagents for the ADVIA Centaur-specific IgE assay were obtained from Bayer Diagnostics (www.bayerdiag.com/Products). The Centaur assay is an allergen-specific assay for measurement of IgE without interference from other types of immunoglobulins or non-specific IgE. The ADVIA Centaur Total-IgE-Test is a Sandwich-Immunoassay starting at two places under application of direct chemiluminescence technology, upon each of which constant amounts of two antibodies for IgE are applied. The first antibody is a goat anti-human-IgE antibody marked

with acridinium ester (Lite-reagent). The second antibody, in the solid phase, is a mouse anti-human-IgE antibody that is covalently bonded to paramagnetic particles. There is a direct proportional relationship between the amount of total IgE in the patient sample and the relative light units measured by the system. Total IgE concentrations up to 3,000 IU/mL can be measured with the test, whereby the lower analytic sensitivity is 1.5 IU/mL. The assay performs with linear reaction, high assay range, and good reproducibility. The assay correlates well with the CAP system and is in agreement with clinical diagnosis (9).

RESULTS

Six months after the beginning of therapy with Omalizumab, a clear decrease of the total IgE concentration versus baseline was demonstrable in all patients (Figure 1). The mean concentration of the total IgE in the serum before the beginning of therapy was $1400.5 \text{ IU/mL} \pm 880.9$; after 6 months, it was $484.5 \text{ IU/mL} \pm 293.9$ ($p < 0.01$, Figure 2). An increase of the total IgE could not be documented in any of the patients (Table 2). On the contrary, a further decrease of the total IgE has been found in three patients who have already been treated with omalizumab for 9 or 24 months.

The subcutaneous administration of omalizumab was very well-tolerated by all patients. In the first and second month after the beginning of the therapy, systemic steroid administration was for the first time no longer necessary for exacerbations for two patients. In the other test subjects, no

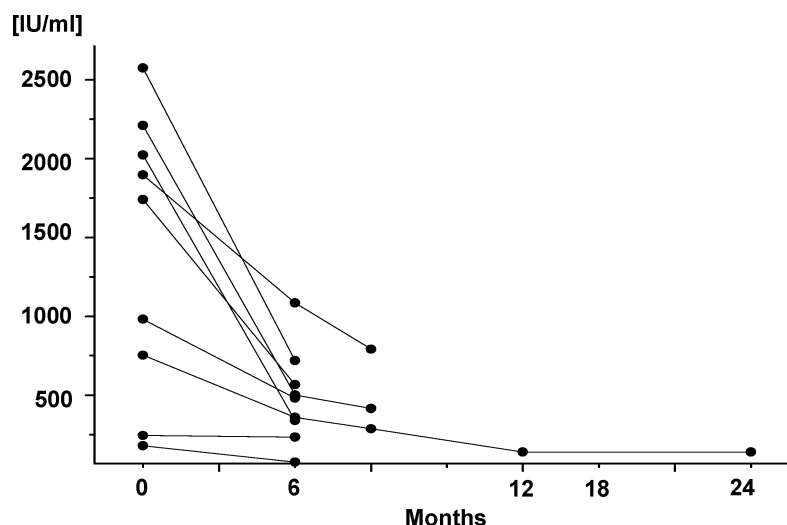


FIGURE 1.—Course of the total IgE in the individual patients with omalizumab therapy.

TABLE 1.—Patient characteristics, therapy parameters, and laboratory variables.

No	Age/ Sex	Diagnosis	Weight (kg)	Dose (mg) 2–4 W.	Duration of Therapy (Months)	IgE (IU/mL) Before Therapy	IgE (IU/mL) 6 M	IgE (IU/mL) 9 M	IgE (IU/mL) 24 M
1	14 m	Asthma IV, Rhinoconjunc- tivitis	41.0	750/4 W. (750/4 W*)	18	982.0	481.6		
2	13 m	Asthma IV, Rhinoconjuncti- vitis, Neurodermitis	28.8	600/4 W. (1150/4 W*)	12	2575.0	719.3		
3	17 f	Asthma IV	62.0	600/4 W. (2000/4 W*)	10	2023.0	338.6		
4	10 f	Asthma IV	43.4	300/4 W.	12	243.9	234.6		
5	8 f	Asthma III-IV	35.3	150/4 W.	10	179.2	75.3		
6	11 f	Asthma III-IV, Rhinoconjunc- tivitis, Neurodermitis, Food Allergy	46.5	300/2 W (1400/4 W*)	9	1896.0	1086.0	881.0	
7	9 f	Asthma III-IV, Rhinoconjunc- tivitis, Insect Sting Allergy	25.0	300/2 W. (300/4 W*)	27	754.1	358.5	287.2	138.7
8	15 m	Asthma III-IV, Rhinoconjunc- tivitis	57.4	450/2 W. (2000/4 W*)	8	2210.0	500.8	415.8	
9	12 f	Asthma IV, Rhinoconjunc- tivitis, Neurodermitis	49.5	300/2 W. (1300/4 W*)	7	1741.0	566.0		

*Calculated dosage according to the formula $(0.016 \times \text{kgKG} \times \text{IgE Base Value IE/mL})$.

more exacerbations have occurred to date. All patients report a clear increase in quality of life, reduction of the medications taken as needed, and no days absent from school. The dosage of the inhaled glucocorticoids could be reduced in six patients and discontinued in another two; in one patient, this therapy was continued unchanged.

DISCUSSION

Current data from clinical studies show that patients with severe allergic asthma experience a significant improvement

with omalizumab (10–12). The early and late allergic reactions are inhibited through the formation of complexes with free circulating IgE, independent of which antigen activates the allergic cascade. Side effects or adverse events indicating an immune complex disease have not been described to date. The data presented so far support a beneficial safety and tolerability profile of omalizumab (1, 13–15).

After subcutaneous injection, omalizumab is slowly reabsorbed. Maximum serum concentrations are reached after 7 to 8 days. The mean bioavailability after subcutaneous administration is 62% (16). The observed maximum plasma concentrations are approximately proportional to the dosage. The mean terminal elimination half-life is at about 3 weeks. Omalizumab reduces the concentration of free IgE in the serum, depending on the dosage and the IgE baseline values.

In dosage-determination studies, it was demonstrated that omalizumab must be given in molar excess (ca. 15 times) to the IgE baseline concentration to reach an adequate reduction of the IgE concentration (17). From that it was concluded that omalizumab must be dosed depending on the individual IgE baseline concentration and the patient's body weight. A multi-level dosage table was developed to simplify the individual dosage and to set an effective reduction of the concentration of free IgE (5). Omalizumab is prescribed to patients with allergic asthma with a serum IgE concentration of 30 to 700 kU/L.

The target value for the mean concentration of free IgE under omalizumab is 25 ng/mL. This value ensures that in at least 95% of the patients, a concentration less than 50 ng/mL is reached, which demonstrated thorough therapeutic benefits in the approval studies (5, 17). The amount of remaining free IgE appears to be especially decisive for therapy success. In recent years, efforts have been made to quantify the free IgE during therapy with omalizumab, with the goal of fine-tuning the intervention for individual patients to attain an optimization of the treatment effects.

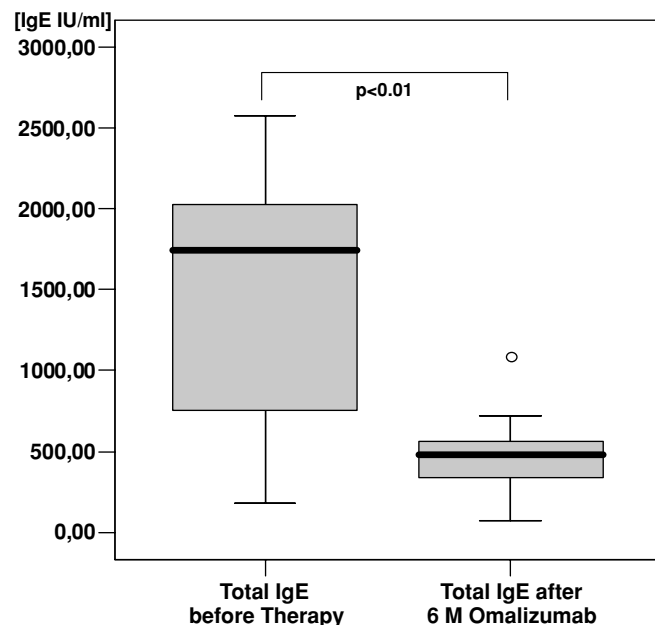


FIGURE 2.—Total IgE before therapy and six months after therapy with omalizumab, (n = 9).

In contrast, according to reports in the literature, the total IgE concentration (which consists of the sum of the concentration of free IgE and IgE-containing immune complexes) increases because IgE in complexes is eliminated via the reticuloendothelial system of the liver with a half-life of about 2 weeks. So, determining the total IgE in the progress of the therapy is not considered meaningful. We could not confirm an increase of the total IgE. In all of the patients, besides the clearly improved quality of life and the reduction of the asthma exacerbation and inhaled glucocorticoid dosage, a lasting reduction of the total IgE concentration was demonstrable. Although we chose in part an around 30% to 50% lower dosage in five patients with IgE values > 700 IU/mL, the clinical therapy successes related here were still apparent with reduction of the total IgE. Because the complexes of omalizumab and IgE have a longer half-life than free IgE, the application of the usual commercial IgE assays yields an apparent IgE increase. Apparently, human IgE is bound to the same epitope as omalizumab in the assay presented here (ADVIA-Centaur). An increase of total IgE is not demonstrable; instead, there is a reduction of the IgE level.

At the present time, the subjective assessment of therapeutic success by the physician seems to be as reliable as the use of objective parameters such as lung function or symptom diaries (18).

It is to be assumed that the IgE production will also be influenced by omalizumab. Hanf *et al.* (19) were able to show that therapy with omalizumab clearly reduced the stimulated release of IgE and the number of circulating B lymphocytes in comparison to placebo. Furthermore, there is a downregulation of the high-affinity IgE receptors on the effector cells under omalizumab. Through this feedback process, the ability of the mast cells to bind to IgE is reduced. These effects indicate an anti-inflammatory potency of the antibodies.

It is our view that the current dosage schemata should serve merely as a preliminary guide and must be modified in the near future. The optimal dosage for the respective patients must be determined individually. However, it has to be considered that it is difficult to draw broad conclusions from the small number of subjects in our study.

The value of total serum IgE should be investigated further as a progress parameter in controlled studies with regard to the sensitivity and specificity of the respective assays. Should our observations be confirmed, e.g. as a reduction of total IgE determined in omalizumab-treated patients by using the ADVIA-Centaur-test, a fine-tuning of an omalizumab therapy would be possible. The establishment of a progress parameter appears to be urgently necessary as an additional guide to therapy beside just the clinical progress itself precisely so that the appropriate dosage of omalizumab is applied in children and adolescents. Our results could provide an initial indication for the development of dosage reduction schemata.

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